

420 Rec'd PCT/PTO 0 6 OCT 1999

MULTIPARTICULATE PHARMACEUTICAL FORM, PARTICLES  
CONSTITUTING IT, METHOD AND PLANT FOR MAKING SAME

5 The invention consists in a multiparticulate  
pharmaceutical form, in particular a multiparticulate  
tablet of the kind based on a plurality of individual  
particles obtained by hot extrusion and individually  
containing the active material.

10 It is also directed to a new industrial product  
consisting of the particles constituting said  
multiparticulate pharmaceutical form.

It is further directed to a method and plant for  
preparing said constituent particles.

15 Solid pharmaceutical forms prepared from a molten  
mixture without solvents of active substances and  
thermoplastics material are disclosed in patent  
US-A-3 432 592, for example, in which they are shaped by  
injection moulding, and patent EP-A-0 190 255, in which  
the molten mass is either injection moulded or extruded.

20 Documents WO-A-9614058 and WO-A-9614059 disclose  
tablets of the kind in question which are prepared by  
compressing a set of individual particles consisting of a  
thermoplastics material matrix within which an active  
substance is dispersed, the particles being obtained by  
25 chopping the filament leaving the die of an extruding  
machine inside which the mixture of the thermoplastics  
material and the active substance has previously been  
subjected to the conditions of hot extrusion; note that  
before the compression step the particles obtained at the  
30 exit from the die can be subjected to a spheroidal  
shaping to give them rounded contours.

35 The major drawback of the above tablets is their low  
rate of disintegration, which makes it very difficult to  
disperse the individual particles within the digestive  
tract.

Also, document EP-A-0 548 356 describes tablets of the kind in question prepared by compressing a mixture containing individual particles obtained by extrusion and spheroidal shaping of an active substance and having a coating to mask the taste and an excipient based on at least one disintegrating agent and/or at least one swelling agent.

The tablets are distinguished by a very high rate of disintegration, leading to dispersion of the individual particles in the mouth, which is rendered acceptable by the presence of their coating.

Finally:

- document DE-A-44 13 350 discloses tablets based on particles obtained by hot extrusion from a mixture of an active substance and a polymer, chopping the extruded filament and shaping the particles, which are optionally coated with a polyacrylate or a cellulose ester, and

- document DE-A-41 22 217 discloses tablets based on particles obtained by wet cold extrusion from a mixture of polymers and active substance, followed by spheroidal shaping and coating.

The most important object of the invention is to provide a multiparticulate pharmaceutical form, in particular a multiparticulate tablet of the kind in question, which has a rate of disintegration such that its disintegration and consequently the dispersion of the individual constituent particles occur in less than 15 minutes in a standard disintegration measuring device, in other words in the upper part of the digestive tract.

Through in-depth research, the applicant company has found that the above object is achieved if the individual particles constituting said multiparticulate pharmaceutical form have a coating based on at least one binding agent, at least one disintegrating agent and optionally at least one active principle.

It follows that the multiparticulate pharmaceutical form in accordance with the invention is characterised in that it consists of a plurality of particles, preferably spheroids having a coating based on at least one  
5 disintegrating agent and at least one binding agent and optionally at least one active substance and consolidated with one another by compression, said particles or spheroids in which an active substance is distributed within a thermoplastics material having been obtained by  
10 hot extrusion without solvent of a mixture of the active

substance with the thermoplastics material and chopping the filament or extrudate leaving the extrusion die.

The particles, preferably the spheroids in accordance with the invention, constituting the  
5 multiparticulate pharmaceutical form of the invention are characterised in that they are the result of chopping a filament or extrudate obtained by hot extrusion without a solvent of a mixture of an active substance and a thermoplastics material and coating the particles  
10 obtained by chopping with a coating including at least one binding agent and at least one disintegrating agent.

It is by virtue of the progressive extraction of the active material from the matrix consisting of the thermoplastics material - which causes the active  
15 substance to pass into the surrounding medium - that the multiparticulate pharmaceutical forms, in particular the multiparticulate tablets of the invention constitute a pharmaceutical form with modified and controlled release.

The curve of the *in vitro* release expressed as a  
20 percentage of the active substance as a function of time is a predetermined essential characteristic of the pharmaceutical form and must be reproduced from one tablet to another.

It is the result of a judicious choice of the  
25 constituent characteristics of the matrix.

In the case of preparing individual particles included in the multiparticulate pharmaceutical form, in particular the multiparticulate tablet, by extruding the mixture of an active substance and a thermoplastics  
30 material constituting the matrix and by chopping the extruded filament at the exit from the die, it is important for the extrusion to be carried out less than 6 hours at 25°C after the mixture to be extruded is made up, at risk of obtaining particles and consequently  
35 tablets for which the curve showing the release of the

active substance as a function of time is modified in the sense of a reduced percentage of active substance released per unit time.

5 This constraint, which is not referred to in the prior art, constitutes a major drawback in that if a mixture ready to be extruded had to be stored for whatever reason for a time exceeding the above limit before it could be extruded, the mixture would have to be regarded as wasted because of the inevitable  
10 deterioration of the curve showing the release of the active substance from the particles obtained by extrusion.

The applicant company has found that it is possible to overcome this drawback by subjecting the mixture of  
15 the active substance and the thermoplastics material to a maturing step.

When said mixture is subjected to this maturing step - whose duration is from 30 minutes to 150 hours at a temperature in the range from 20°C to 70°C - its  
20 extrusion yields particles which have an active principle release curve which is stabilised provided that the time lapse between the preparation of the mixture and its extrusion does not exceed approximately 7 days.

It is found that this - stabilised - active  
25 principle release curve represents slower kinetics than are obtained with particles with the same composition but extruded immediately after making up the mixture, with no maturing step; this means that at a given time the percentage of active substance released by the particles  
30 prepared by extrusion after maturing is less than that released by particles extruded without maturing.

For the two curves to be superposed, the mixture subjected to a maturing step before extrusion must contain a greater concentration of active substance.

35 The maturing phase therefore has an additional

5 advantage in that the particles obtained by the method of the invention including the maturing phase introduce into the organism an increased quantity of active substance for the same volume or even a reduced volume and at an equivalent rate.

It follows that the method in accordance with the invention of making particles, in particular spheroids with a constant diameter in the range from 0.5 mm to 2 mm, including an active substance and having a  
10 controlled and predetermined active substance release curve, which method includes successively:

- a step of selecting an active substance and a thermoplastics material, including at least one polymer excipient and at least one plasticiser,
- 15 - a step of mixing the active substance and the thermoplastics material,
- a step of extruding the mixture without solvent at a controlled temperature to produce at least one extruded filament or extrudate, and
- 20 - a step of chopping the extrudate into particles, is characterised in that it includes a step of maturing the mixture of the active substance and the thermoplastics material before extrusion at a temperature and for a time chosen according to the characteristics of  
25 the intended active principle release curve and respectively in the range from 20°C to 70°C and in the range from 30 minutes to 150 hours, whereby it becomes possible to store the mixture of the active substance and the thermoplastics material for up to 7 days before  
30 extruding it and to increase the quantity of active substance for a given release curve without increasing the volume of the tablet.

As a result of this, the particles constituting the multiparticulate pharmaceutical form, in particular the  
35 multiparticulate tablet of the invention, are preferably

in the form of spheroids, i.e. have rounded contours.

The spheroidal shaping constitutes an additional process step generating an additional cost; moreover, it is possible only if the extrudate retains physical properties such that it can be formed to a spheroidal shape at the working temperature.

The applicant company has found that it is possible to obtain the particles in accordance with the invention directly in spheroidal form at the exit from the die provided that the cutters in the chopping device at the exit from the die have the shape described later and shown in figures 1 and 2.

It follows that the plant of the invention for making spheroids in accordance with the invention comprises an extruding machine having a tool for chopping the extruded filament or extrudate at the exit from the extrusion die fitted with cutters having the shape shown in figures 1 and 2.

The invention will be better understood with the aid of the additional description that follows and the non-limiting examples which concern advantageous embodiments of the invention.

Consequently, the following process or an equivalent process is used to make the particles, in particular the spheroids, in accordance with the invention and the multiparticulate pharmaceutical form, in particular the multiparticulate tablet containing them.

First an active substance and the constituents of a thermoplastics material, namely at least one polymer and at least one plasticiser, are selected.

The active substance, which must be stable from the physical point of view and from the chemical point of view at the softening point of the thermoplastics material, is advantageously chosen from the group comprising gastrointestinal sedatives, antacids,

analgesics, anti-inflammatories, coronary vasodilators, peripheral and cerebral vasodilators, anti-infective agents, antibiotics, antiviral agents, antiparasitic agents, anti-cancer agents, anxiolytics, neuroleptics, 5 central nervous system stimulants, antidepressants, antihistamines, antidiarrhoeal agents, laxatives, food supplements, immunosuppressors, cholesterol-lowering agents, hormones, enzymes, antispasmodics, antianginals, drugs influencing cardiac rhythm, drugs used in the 10 treatment of arterial hypertension, anti-migraine agents, drugs influencing the coagulation of blood, antiepileptics, muscle relaxants, drugs used in the treatment of diabetes, drugs used in the treatment of thyroid dysfunction, diuretics, anti-anorexia agents, 15 anti-asthmatic agents, expectorants, antitussives, mucoregulators, decongestants, hypnotics, anti-emetics, haematopoietics, uricosurics, plant extracts, contrast agents.

Its particle size range must be compatible with 20 homogeneous dispersion within the thermoplastics material.

Its particle size range is advantageously from 0.1  $\mu\text{m}$  to 500  $\mu\text{m}$  and preferably from 1  $\mu\text{m}$  to 100  $\mu\text{m}$ .

The polymer is a thermoplastics polymer whose 25 softening point is preferably in the range from 10°C to 50°C below the melting point of the active substance; it is advantageously chosen from the group comprising ethyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, 30 hydroxypropylmethyl cellulose acetosuccinate, cellulose acetobutyrate, cellulose acetopropionate, cellulose acetophthalate, hydroxypropylmethyl cellulose phthalate, microcrystalline cellulose, sodium carboxymethyl cellulose, polymethacrylate, polyethylene oxides, 35 polyvinyl pyrrolidones, cross-linked starch, lactic acid,



polyvinyl acetate, polyvinyl alcohol and vinyl acetate resins.

It is advantageously in the form of a powder.

5 The plasticiser is preferably chosen from those which are liquids and more particularly from the group comprising ethyl phthalate, dibutyl sebacate, triacetine, triethyl citrate, dioctyl phthalate, diphenyl phthalate, dibutyl phthalate, polyethylene glycol and acetylated monoglycerides.

10 The active substance and thermoplastics polymer powders are mixed and the plasticiser is incorporated into the mixture.

A planetary mixer can be used to perform the mixing or preferably a double-jacket fast shear type mixer.

15 Collette mixers can be used.

The temperature of the constituents of the mixture during the mixing operation is in the range from 20°C to 70°C.

20 The respective proportions of the active substance, the polymer and the plasticiser are preferably as follows:

- active substance: 5 wt% to 80 wt%,
- polymer: 5 wt% to 80 wt%, and
- plasticiser: 1 wt% to 25 wt%.

25 The mixture advantageously includes from 0.1 wt% to 1 wt% colouring agent.

The mixture obtained as described above is subjected to an extrusion operation.

30 However, in accordance with the invention, it is first subjected to a maturing step.

The maturing step consists in maintaining the mixture at a temperature in the range from 20°C to 70°C, preferably in the range from 35°C to 70°C, for 30 minutes to 150 hours, advantageously in a ventilated tray type oven.

35

The duration of the maturing step can be reduced to less than 10 hours provided that the mixture is agitated slowly in the mixer during the maturation step.

Because of the maturing step, the mixture consisting  
5 of the thermoplastics material and the active substance can be stored for up to 7 days before the extrusion step.

The extrusion step is carried out in an extruding machine, for example a single-screw machine, into whose kneading area the mixture is introduced in powder form.

10 In the kneading area, the mixture is subjected to the following temperature and pressure conditions:

- temperature: from 20°C to 200°C, and
- pressure: from 10 bars to 160 bars.

It remains in the kneading area for 2 to 6 minutes.

15 The temperature, pressure and duration parameters are chosen according to the characteristics of the polymer in the mixture and the size of the spheroids to be obtained.

Because of the conditions that apply in the kneading  
20 area, the original powder mixture is converted into a fluid paste in which the particles of active substance remain in the solid state.

The fluid paste is extruded through a die whose diameter depends on the required size of the spheroids  
25 and is in the range from 0.5 mm to 2.0 mm.

At the exit from the die, the extruded mixture is in the form of a filament or an extrudate whose diameter exceeds the diameter of the die by 20% to 150% because of expansion; the filament or extrudate is solidified and  
30 stiffened by cooling, for example using a jet of air.

It is possible to use a multiple die that produces a plurality of filaments or extrudates.

The filament exit rate is from 10 to 80 g/minute and depends on the rotation speed of the screw.

35 The filament or extrudate obtained at the exit from

the die is chopped by a rotary chopping tool comprising one or more cutters; the chopping tool is disposed so that the distance between the face of the die across which the cutters are moved by the rotation of the tool and the surface of said cutters is from 0.04 mm to 0.15 mm.

According to the invention, the cutters have the shape shown in figures 1 and 2.

Figure 1 is a plan view of a cutter C in accordance with the invention and figure 2 is an end view of it as seen in the direction of the arrow II-II in figure 1.

As shown in figure 1, the cutter C, which is generally rectangular with two longer sides  $m_1$  and  $m_2$  and two shorter sides  $n_1$  and  $n_2$ , has:

- a solid part  $C_1$  by means of which it is fixed to the chopping tool, not shown, for example by screws, not shown, for which two threaded holes  $T_1$  and  $T_2$  are provided, and

- a part  $C_2$  which is recessed from the longer side  $m_2$  towards the longer side  $m_1$  which includes the cutting edge T of the cutter, to a distance  $d$  from the side  $m_1$  which is less than 1 mm, so that the surface of the cutter consisting of the face shown of the part  $C_1$  is extended along the side  $m_1$  in the part  $C_2$  by a strip B of width  $d$ .

Figure 2 shows clearly the recessed shape of the part  $C_2$ , the cutting edge on the side  $m_1$  and the strip B of width  $d$ .

The arrow  $F_1$  in figure 1 shows the direction the cutters move when the chopping tool rotates.

Accordingly, as the chopping tool rotates, the cutting edges T of the cutters C impinge on the filament, not shown, leaving the die, not shown, and chop the filament into successive particles.

It is because, in accordance with the invention, the

width of the strip B is less than 1 mm that chopping the filament or extrudate leaving the die produces particles of spheroidal shape directly, with no additional spheroidal shaping step, the precise value of  $d$  being  
5 determined by the diameter of the hole in the die and the rate at which the extruded filament leaves it.

The relationship between the value of  $d$ , the diameter of the hole in the die and the exit rate of the extrudate is determined empirically in each individual  
10 case.

The greatest dimension of the spheroidal particles obtained is generally in the range from 0.5 mm to 2 mm.

This dimension is a function of the rotation speed of the extrusion screw shaft, the temperature gradient in  
15 the extrusion area, and the temperature and dimensions of the die. The rotation speed of the screw shaft is preferably in the range from 1 rpm to 90 rpm. The temperature gradient in the extrusion area and the temperature of the die are preferably in the range from  
20 20°C to 200°C. The diameter of the die orifice is preferably in the range from 0.5 mm to 2 mm.

The rotation speed of the chopping tool is fixed by the rate at which the extruded filament leaves the die orifice and is preferably in the range from 40 rpm to  
25 1 500 rpm.

The spheroidal particles obtained at the exit from the die are coated with a coating including at least one disintegrating agent; the coating can also include a binding agent; it can further contain an active  
30 substance.

A turbine or a fluidised air bed can be used for this purpose.

Firstly, the binding agent is sprayed on in the form of a 10 wt% to 30 wt% solution in an appropriate and  
35 pharmaceutically acceptable solvent, preferably alcohol

or water. From 1 wt% to 50 wt% of disintegrating agent relative to the weight of the spheroids is then fixed in the powder state to the spheroids covered with binding solution.

5       The spheroidal shape of the particles is essential for obtaining effective coating.

The particle size range of the disintegrating agent is preferably from 1  $\mu\text{m}$  to 100  $\mu\text{m}$ .

10       The disintegrating agent is chosen from the group comprising cross-linked polyvinyl pyrrolidone, modified starch and cross-linked sodium carboxymethyl cellulose, and the binding agent is preferably chosen from the group comprising polyvinyl pyrrolidone, polyethylene glycol, polymethacrylate and hydroxypropylmethyl cellulose.

15       The total mass of the coating is preferably 2 wt% to 20 wt% relative to the mass of the spheroidal particles.

20       The multiparticulate pharmaceutical form, in particular the multiparticulate tablet, according to the invention, is prepared from the spheroids obtained in the above way.

Compression techniques familiar to the skilled person can be used for this purpose.

25       The parameters of the compression step are set so that the hardness of the resulting tablets is in the range from 30 N to 70 N.

#### EXAMPLE 1

This example concerns spheroids containing sodium diclofenac as the active substance.

30       It includes an assessment of the effect of the maturing step on the rate of release of the active substance from the spheroids.

35       The polymer chosen for constituting the thermoplastics material is a polymer of ethyl cellulose having a softening point of 130-133°C (glass transition temperature).

It is not soluble in an aqueous medium, or only slightly soluble, and the viscosity of a 5% (m/m) alcohol solution of the polymer at 25°C is from 5 mPa to 8 mPa. This polymer is sold under the name EC N7NF by Aqualon/Hercules.

The plasticiser used was diethyl phthalate.

Hereinafter, the active substance, the polymer and the plasticiser are designated by the following abbreviations:

- DFC: sodium diclofenac,
- EC N7NF: ethyl cellulose polymer, and
- DEP: diethyl phthalate.

The centesimal composition of the mixture for preparing the spheroids was as follows:

- DFC: 25 wt%,
- EC N7NF: 65 wt%, and
- DEP: 10 wt%.

To assess the effect of the maturing step on the curve showing release of the active substance from spheroids obtained by extruding the above mixture, nine samples A1, A2, B1, B2, B3, B4, C1, C2 and C3 of the mixture were prepared.

Samples A1 and A2 were maintained at room temperature for four hours and two days, respectively, before extrusion.

Samples B1 through B4 were subjected to a maturing step at 70°C in an oven for four hours, one day, two days and three days, respectively.

Samples C1 through C3 were subjected to a maturing step at 40°C in an oven for one day, two days and three days, respectively.

The nine samples were extruded using a single-screw extruding machine and then chopped, the extrusion parameters being as follows:

- temperature in the extrusion area: 130°C to 170°C,

- screw speed: from 20 rpm to 75 rpm,
- pressure in the extrusion area: from 25 bars to 130 bars, and
- die orifice diameter: 1 mm.

5           The extruded filament or extrudate was chopped using a chopping tool with cutters in accordance with the invention, the rotation speed of the chopping tool being adjusted to obtain the best possible hot spheroidal shaping. This speed was 756 rpm, for example.

10           The particle size range of the spheroids obtained was from 1.2 mm to 1.6 mm.

          Using measuring apparatus designated 'Apparatus I' in the American Pharmacopoeia (USP XXIII) and 'Rack apparatus' in the European Pharmacopoeia (3<sup>rd</sup> edition),  
15           the conditions of use of the apparatus being 1 litre of pH 7.0 buffer solution at 37°C per reactor and a rotation speed of 100 rpm, the percentages of active substance released *in vitro* after 0.5 hour, 1 hour, 1.5 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours and 8  
20           hours were determined for the spheroids obtained from each of samples A1 through C3 processed as indicated above.

          The values obtained are set out in Table I.

**TABLE I**

*room temp*      *70°C*      *40°C*

| H<br>○    | Percentage of active substance released in the<br><i>4hrs 2day 4hrs case of 2day 3day</i><br>the samples <i>1 day 2 day 3 day</i> |      |      |      |      |      |      |      |      |
|-----------|---|------|------|------|------|------|------|------|------|
|           | A1  | A2   | B1   | B2   | B3   | B4   | C1   | C2   | C3   |
| 0.5 hour  | 31.5  | 29.6 | 12.4 | 8.8  | 6.0  | 4.7  | 17.7 | 10.6 | 9.1  |
| 1 hour    | 44.1  | 41.1 | 22.9 | 20.2 | 12.7 | 9.7  | 30.6 | 19.8 | 17.8 |
| 1.5 hours | 53.2  | 50.8 | 31.7 | 32.3 | 21.3 | 16.9 | 41.9 | 28.1 | 26.1 |
| 2 hours   | 62.8  | 57.4 | 39.4 | 41.6 | 29.4 | 23.9 | 49.7 | 35.6 | 32.6 |
| 3 hours   | 72.8  | 63.5 | 54.5 | 59.0 | 42.6 | 36.3 | 62.9 | 49.9 | 44.9 |
| 4 hours   | 77.1  | 74.5 | 63.3 | 68.4 | 54.2 | 47.5 | 70.1 | 57.7 | 55.0 |
| 5 hours   | 82.7  | 79.4 | 69.8 | 74.1 | 61.5 | 55.7 | 73.1 | 64.9 | 61.1 |
| 6 hours   | 85.6  | 82.3 | 71.9 | 75.5 | 66.9 | 62.0 | 76.1 | 69.0 | 66.5 |
| 7 hours   | 87.3  | 85.5 | 74.7 | 77.2 | 71.7 | 66.2 | 80.3 | 72.5 | 70.2 |
| 8 hours   | 86.5  | 85.1 | 76.2 | 78.7 | 72.9 | 69.5 | 80.4 | 75.2 | 72.5 |

5 Column H shows the measurement time relative to the start of the experiment.

The conclusion that can be drawn from the values set out in the table is that the maturing treatment slows the kinetics of dissolving the active substance.

#### EXAMPLE 2

10 This example shows how the maturing step stabilises the curve showing release or dissolution of the active principle from spheroids when the matured mixture was stored before it was extruded, the mixture being the same as that described in example 1, i.e. a mixture

15 comprising:

- DFC: 25 wt%,
- EC N7NF 65 wt%, and
- DEP: 10 wt%.

20 Three samples D1, D2 and D3 were prepared from the mixture.

Sample D1 was kept at room temperature for four



hours before it was extruded, with no maturing step.

Sample D2 was subjected to a maturing step of two days at 40°C and then extruded.

5 Sample D3 was subjected to the same maturing step as sample D2, stored at room temperature for four days and then extruded.

The specifications of the extrusion treatment were those set out in example 1.

10 The particle size range of the spheroids obtained was 1.2 mm to 1.6 mm.

Using the same procedure as example 1, the percentages of active substance released *in vitro* after 0.5 hour, 1 hour, 1.5 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours and 8 hours were determined.

15 The values obtained are set out in Table II.

TABLE II

| H         | Percentage of active substance released in the case of the samples |      |      |
|-----------|--|------|------|
|           | D1   | D2   | D3   |
| 0.5 hour  | 25.8   | 11.4 | 9.5  |
| 1 hour    | 40.0   | 23.5 | 19.0 |
| 1.5 hours | 48.6   | 34.5 | 27.7 |
| 2 hours   | 55.8   | 41.8 | 35.9 |
| 3 hours   | 64.6   | 56.1 | 49.4 |
| 4 hours   | 73.5   | 65.7 | 60.2 |
| 5 hours   | 75.5   | 69.8 | 67.1 |
| 6 hours   | 76.8   | 73.7 | 71.0 |
| 7 hours   | 81.3   | 77.7 | 73.2 |
| 8 hours   | 79.9   | 78.2 | 75.1 |

20 The results set out in Table II show that the active substance release curves stabilised when the mixture from which the spheroids were obtained had been subjected to a

maturing step before extrusion, making it possible to store a mixture of this kind before extrusion.

### EXAMPLE 3

5 This example concerns a multiparticulate tablet with modified release containing sodium diclofenac as the active substance.

The following powder mixture was prepared for the extrusion step:

- 10 - DFC: 40 wt%,
- EC N7NF: 52 wt%,
- DEP: 8 wt%, and
- E110 colouring agent: 0.2 wt%.

The powder mixture was extruded using a single-screw extruder.

15 The extrusion parameters were as follows:

- temperature of the kneading area and the die:  
130°C to 170°C,
- screw speed: 50 rpm,
- pressure in the kneading area: 25 bars to 70 bars,
- 20 - chopping tool rotation speed: 746 rpm, and
- die orifice diameter: 1 mm.

The spheroids obtained were used to prepare multiparticulate tablets containing a 100 mg dose of DFC.

The spheroids were first coated.

25 For this purpose, the spheroids were placed in a turbine.

A binder consisting of an alcohol solution of PVP K30 polyvinyl pyrrolidone sold by BASF was first applied to them.

30 KOLLIDON CLM (trade mark) disintegrating agent sold by BASF was then applied to the spheroids treated in the above manner. Three samples of spheroids were prepared to which 10 wt%, 15 wt% and 20 wt% of the disintegrating agent relative to the mass of the spheroids were  
35 respectively applied.

Multiparticulate tablets were prepared from the three samples of spheroids obtained in this way, and from a sample of uncoated spheroids, by compression in a SVIAC PR 6 (trade mark) rotary compression machine sold by SVIAC, using bevelled punches with a diameter of 10 mm.

The following were determined for the tablets obtained in this way:

- the average mass,
- the thickness,
- the hardness,
- the friability, and
- the disintegration time (as per the 1997 European Pharmacopoeia, Section 2.9.1).

The values obtained in this way are set out in Table III, which also shows the theoretical mass and quantity of active material per gram of spheroids (titre).

TABLE III

|                          | Uncoated<br>spheroids | 10% coated<br>spheroids | 15% coated<br>spheroids | 20% coated<br>spheroids |
|--------------------------|-----------------------|-------------------------|-------------------------|-------------------------|
| Titre                    | 411.9 mg/g            | 382.6 mg/g              | 363.3 mg/g              | 343.0 mg/g              |
| Theoretical<br>mass      | 242.78 mg             | 261.37 mg               | 275.25 mg               | 291.55 mg               |
| Average mass             | 242.9 mg              | 255.2 mg                | 276.33 mg               | 294.83 mg               |
| C.V. mass                | 2.43%                 | 2.31%                   | 1.90%                   | 2.14%                   |
| Hardness                 | 45.8 N                | 41.9 N                  | 39.4 N                  | 37.8 N                  |
| Thickness                | 3.15 mm               | 3.21 mm                 | 3.53 mm                 | 3.86 mm                 |
| Friability               | 0.02%                 | 0.55%                   | 0.18%                   | 0.36%                   |
| Disintegra-<br>tion time | > 15 min              | 6 min 40 s              | 7 min 40 s              | 12 min 30 s             |

5 The results set out in Table III show that the  
disintegration speed of the tablets increased with the  
proportion of disintegrating agent in the coating.

The required disintegration speed could be obtained  
with less than 20% disintegrating agent.

EXAMPLE 4

10 This example concerns a multiparticulate tablet with  
modified release including pseudoephedrine as the active  
substance.

The following mixture was prepared:

- 15 - Pseudoephedrine: 40 wt%,  
- EC N7NF: 52 wt%, and  
- DEP: 8 wt%.

Spheroids were prepared from the above powder  
mixture using a single-screw extruder and the following  
extrusion parameters:

- 20 - temperature of the extrusion area and the die:  
130°C to 170°C,  
- screw speed: 72 rpm,

- pressure in the extrusion area: 40 bars to 90 bars,
- chopping tool rotation speed: 700 rpm, and
- die orifice diameter: 1 mm.

5       The spheroids obtained were used to prepare multiparticulate tablets containing a 240 mg dose of pseudoephedrine.

      The spheroids were first coated.

10       For this purpose, the spheroids were placed in a turbine.

      A binder consisting of an alcohol solution of PVP K30 polyvinyl pyrrolidone sold by BASF was first applied to them.

15       KOLLIDON CLM (trade mark) disintegrating agent sold by BASF was then applied to the spheroids treated in the above manner. Four samples of spheroids were prepared in this way, to which 5 wt%, 10 wt%, 15 wt% and 20 wt% of disintegrating agent relative to the mass of the spheroid were respectively applied.

20       Multiparticulate tablets were prepared from the resulting four samples of spheroids, and from a sample of uncoated spheroids, by compression in SVIAC PR 6 (trade mark) rotary compression machine sold by SVIAC, using bevelled punches with a diameter of 14 mm.

25       The following were determined for the tablets obtained in this way:

- the average mass,
- the thickness,
- the hardness,
- 30       - the friability, and
- the disintegration time (as per the 1997 European Pharmacopoeia, Section 2.9.1).

      The values obtained in this way are set out in Table IV, which also shows the theoretical mass and quantity of  
35       active material per gram of spheroids (titre).

TABLE IV

|                        | Uncoated<br>spheroids | 5% coated<br>spheroids | 10% coated<br>spheroids | 15% coated<br>spheroids | 20% coated<br>spheroids |
|------------------------|-----------------------|------------------------|-------------------------|-------------------------|-------------------------|
| Titre                  | 384.6 mg/g            | 354.8 mg/g             | 332.4 mg/g              | 322.5 mg/g              | 308.2 mg/g              |
| Theoretical mass       | 624.02 mg             | 676.44 mg              | 722.02 mg               | 744.19 mg               | 778.72 mg               |
| Average mass           | 622.5 mg              | 683.4 mg               | 729.0 mg                | 744.3 mg                | 771.9 mg                |
| C.V. mass              | 1.37%                 | 1.21%                  | 1.17%                   | 1.36%                   | 1.18%                   |
| Hardness               | 41.2 N                | 41.1 N                 | 39.5 N                  | 28.1 N                  | 37.5 N                  |
| Thickness              | 4.82 mm               | 5.08 mm                | 5.28 mm                 | 5.55 mm                 | 5.66 mm                 |
| Friability             | 0.02%                 | 0.01%                  | 0.21%                   | 2 cp cracked            | 4 cp cracked            |
| Disintegration<br>time | > 15 min              | 4 min 07 s             | 13 min 27 s             | 8 min 58 s              | > 15 min                |

5           The results set out in Table IV show that the disintegration speed of the tablet increased with the proportion of disintegrating agent in the coating, except for the sample with 15 wt% disintegrating agent, which was weaker from the point of view of its hardness.

10           The required disintegration speed could be obtained with approximately 10% disintegrating agent.

EXAMPLE 5

15           This example concerns a multiparticulate tablet with modified release containing sodium diclofenac as the active substance.

          The following powder mixture was prepared for the extrusion step:

- 20           - DFC:           40 wt%,  
          - EC N7NF:       52 wt%, and  
          - DEP:           8 wt%.

          The powder mixture was extruded using a semi-industrial single-screw extruder.

          The extrusion parameters were as follows:

- temperature in the kneading area and the die:  
130°C to 170°C,
- screw speed: 50 rpm,
- pressure in the kneading area: 150 bars to  
5 190 bars,
- chopping tool rotation speed: 7 000 rpm to  
8 000 rpm, and
- die orifice diameter: 1 mm.

10 The spheroids obtained were used to prepare  
multiparticulate tablets containing a 100 mg dose of DFC.  
The spheroids were first coated.

For this purpose, the spheroids were placed in a  
turbine.

15 A binder consisting of a solution in alcohol of  
PVP K30 polyvinyl pyrrolidone sold by BASF was first  
applied to them.

20 10 wt% relative to the mass of the spheroids of  
KOLLIDON CLM (trade mark) disintegrating agent sold by  
BASF was then applied to the spheroids treated in the  
above manner.

Multiparticulate tablets were prepared from the  
resulting spheroids by compression in a SVIAC PR 6 (trade  
mark) rotary compression machine sold by SVIAC, using  
flat punches 10 mm in diameter.

25 The parameters determined for the tablets obtained  
in this way are set out in Table V.

TABLE V

| Parameter           | Multiparticulate tablet of the invention containing a 100 mg dose of DFC |
|---------------------|--|
| Titre (mg/g)        | 357.9  |
| Average mass (mg)   | 279.4 $\pm$ 3.6  |
| Hardness (N)        | 45.10 $\pm$ 5.63   |
| Thickness (mm)      | 3.58 $\pm$ 0.03  |
| Friability (%)      | 0.09   |
| Disintegration time | 9 min 44 s   |

5           The tablets were subjected to pharmacokinetic trials in six healthy subjects.

          Table VI below sets out the results for the principal pharmacokinetic parameters observed in healthy subjects after administering a multiparticulate DFC  
10   tablet containing a 100 mg dose of active substance:

          -  $t_{max}$  (h): the time in hours after which the concentration of active principle in the serum reached a maximum,

          -  $C_{max}$  ( $\mu\text{g/l}$ ): the value of the maximum active  
15   principle concentration reached at  $t_{max}$ , expressed in  $\mu\text{g}$  of active principle per litre of serum, and

          - 0-12 hours AUC ( $\mu\text{g.h/l}$ ): the area under the curve of the active principle concentration in the serum as a function of time up to the last sample taken, i.e. over a  
20   period of 12 hours.



TABLE VI

| Parameter                            | Multiparticulate tablet of the invention containing a 100 mg dose of DFC |
|--------------------------------------|--|
| Tmax (h)                             | 1.25   |
| Cmax ( $\mu\text{g/l}$ )             | $372 \pm 58$   |
| 0-12 AUC hours ( $\mu\text{g.h/l}$ ) | $1\ 176 \pm 163$   |

5           The results set out in Table VI confirm that  
disintegration of the tablet followed by dissolution and  
absorption of the sodium diclofenac contained in the  
spheroids occurred in the upper part of the digestive  
tract of healthy adult subjects. The low variation  
10 between subjects indicated the good quality of the DFC  
formulation of the invention.